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DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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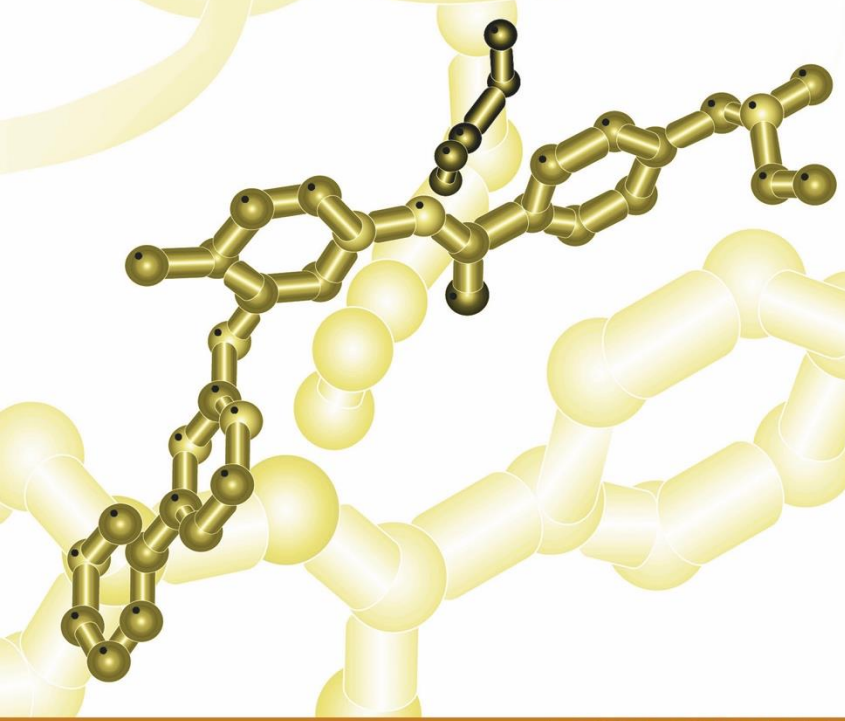

New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
January 15-17, 2024

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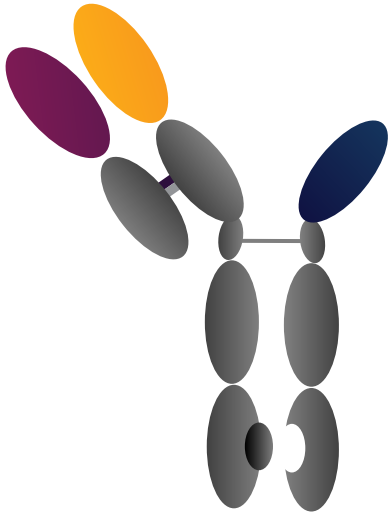
Disclosures of Ryan Jacobs

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AstraZeneca	X		X		X	X	
TeneoBio	X						
Pharmacyclics	X		X		X		
Lilly	X		X				
Abbvie	X		X		X		
Genentech			X				
Beigene					X	X	
SecuraBio					X		
Gilead					X		

TNB-486 (now AZD0486), a Novel CD19xCD3 T-cell Engager (TCE), in Relapsed/Refractory NHL: Interim Results From an Ongoing Phase I Study



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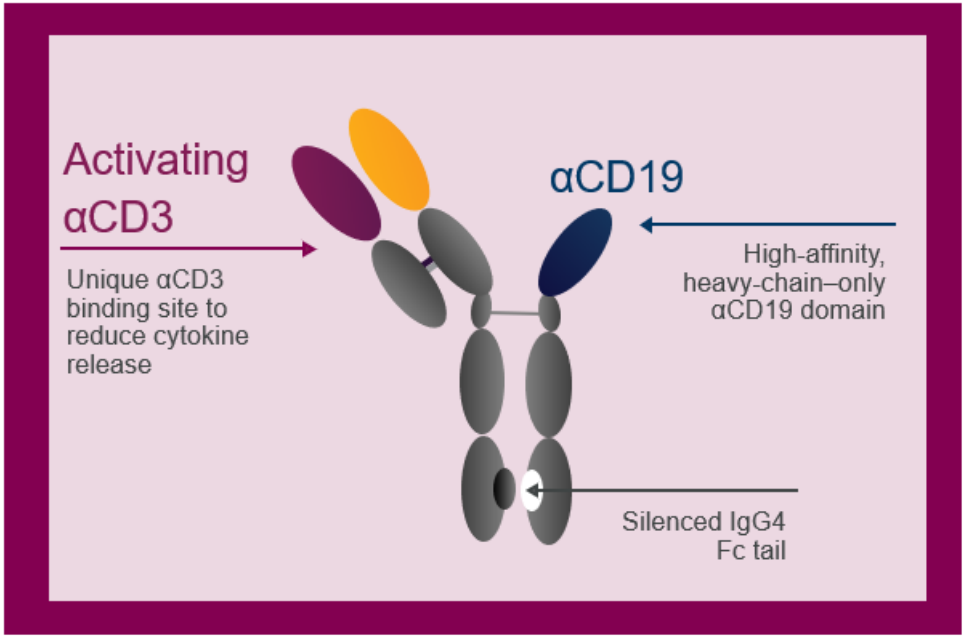
Background

- Despite treatment advances including the use of CAR T-cell therapies and CD20-directed T-cell engagers (TCE), significant **unmet need** remains for patients with **R/R HL after ≥2 lines of prior therapy**, with progressive **shortening of PFS** with each line of treatment
- CD20 antigen loss following multiple rounds of CD20-directed therapies is associated with poor prognosis
- TNB-486 is a **CD19 x CD3** fully **human IgG4 TCE** rationally **designed** to maintain **high efficacy while reducing toxicity**

Figure 1. AZD0486 Structure

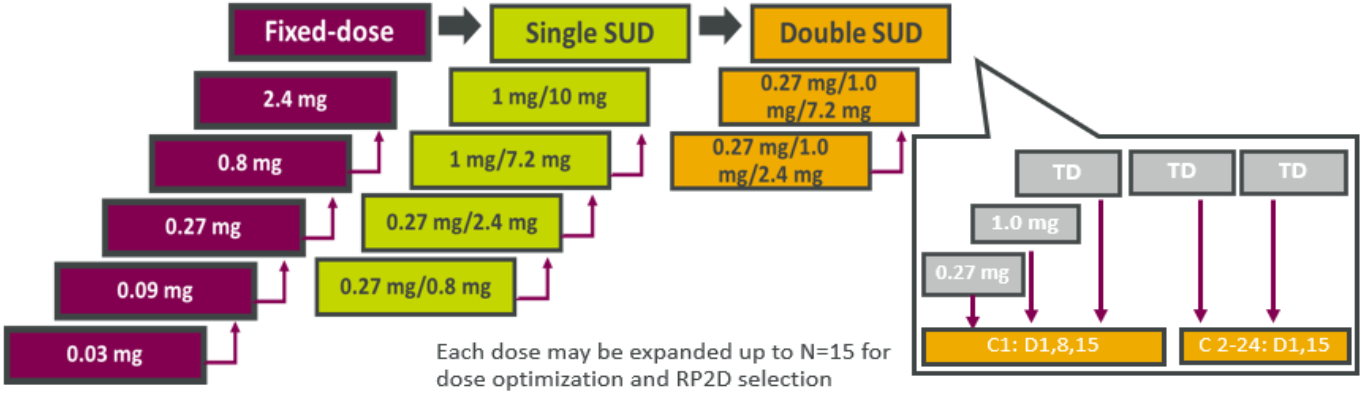


TNB486.001 (NCT04594642[1]): an ongoing Phase 1, Global, Dose-escalation and Optimization Trial in R/R B-NHL

Key Eligibility

- Age ≥18 years
- CD19+ R/R B-NHL
- ≥ 2 prior lines of therapy (anti-CD19 directed regimens and prior TCEs allowed)
- ECOG PS ≤ 2
- ≥ 1 measurable lesion
- No active CNS disease

Study Design



Study Endpoints

- **Primary**: safety, tolerability, PK
- **Secondary**: anti-tumor activity (RECIL 2017[2])

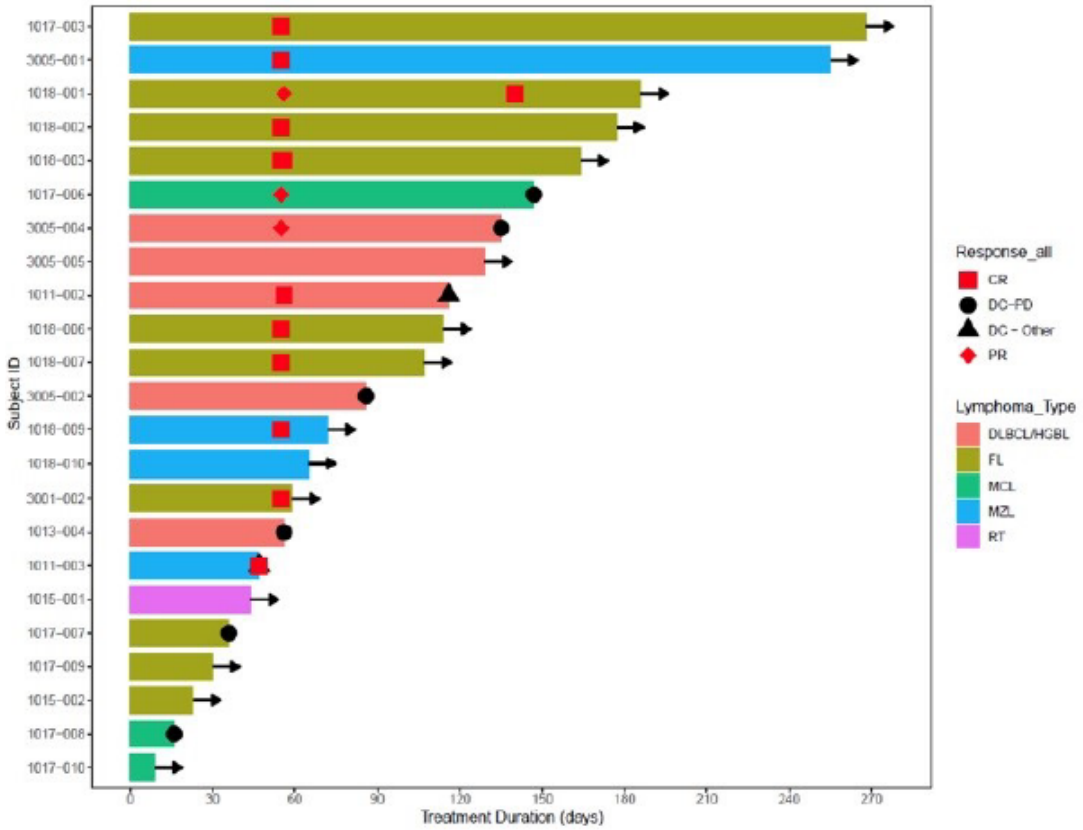
Treatment Schedule

- TNB-486 administered by IV infusion every 2 wks (28-day cycles), up to 2 yrs
- In patients with CR after cycle 6, treatment may be given every 4 wks

B-NHL, B-cell non-Hodgkin lymphoma; CD19, cluster of differentiation 19; CNS, central nervous system; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance status; IV, intravenous; OS, overall survival; PK, pharmacokinetics; RECIL, Response evaluation criteria in lymphoma; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory; SUD, step-up dosing. TD, target dose; 1. NCT04594642. Available at: https://clinicaltrials.gov/ct2/show/NCT04594642 . 2. Younes, et al. Ann Onc 2017.

ASH 2022

Gender, n (%)	
Female	12 (44)
Male	15 (56)
Age, Median (Range)	68 (38 - 85)
Lymphoma Subtype, n (%)	
Follicular	12 (44)
Diffused Large B-cell/High Grade	7 (26)
Marginal Zone	4 (15)
Mantle Cell	4 (15)
Prior Lines of Therapy, Median (Range)	4 (2-21)
>3 Prior Lines of Therapy	15 (56)
Prior CAR-T	5 (19)
Prior HSCT	4 (15)
Lymphoma Stage at Diagnosis, n (%)	
Unknown	3 (11)
Stage I - II	3 (11)
Stage III - IV	21 (78)
ECOG, n (%)	
0	8 (30)
1	17 (63)
2	2 (7)
CD20-negative, n (%)	6 (22)



J Zhou et al. ASH 2022.

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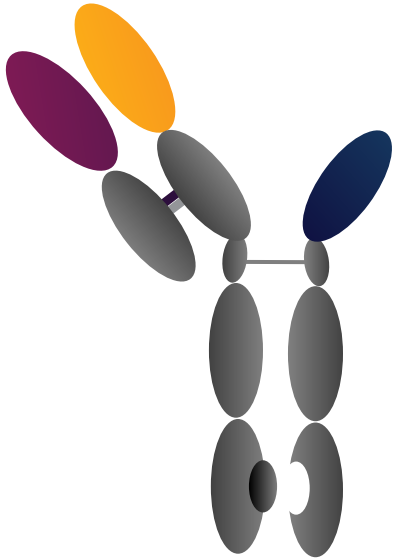
- ORR at >800 uG was 72% (13/18); CR rate 61%
- 2/3 patients previously treated with CAR T achieved a CR
- 3/4 MZL patients achieved CR
- For DLBCL ORR 40%
- One DLBCL patient achieved an MRD negative CR
  - First CR for this patient after 5 prior lines of therapy including CAR T



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EHA 2023

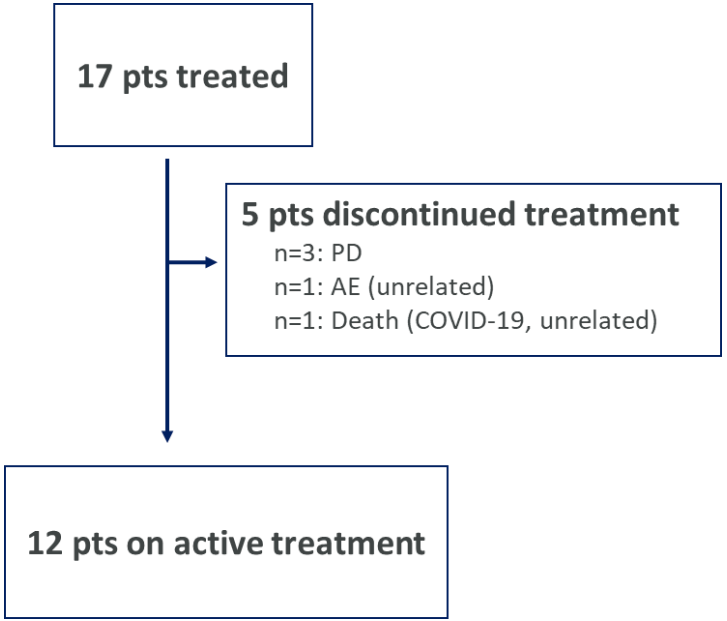
High Complete Response Rate with TNB-486, a Novel CD19xCD3 T-cell Engager (TCE), in Relapsed/Refractory (R/R) Follicular Lymphoma (FL): Interim Results From an Ongoing Phase I Study

Ryan Jacobs, MD[1], Ranjit Nair, MD[2], Seok-Goo Cho, MD, PhD[3], Sumana Devata, MD[4], Sameh Gaballa, MD[5], Dok Hyun Yoon, MD, PhD[6], Don A. Stevens, MD[7], Jin Seok Kim, MD, PhD[8], Nirav Niranjan Shah, MD[4], Denise Brennan[9], Jason Law, MD[9], Robin Lesley PhD[10], Rob Chen, MD[11], Alessandra Forcina, MD[11], Ben Buelow, MD, PhD[12], Jing-Zhou Hou, MD, PhD[13]

[1]Atrium Health Levine Cancer Institute, Charlotte, NC, USA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of South Korea; [4]Medical College of Wisconsin, Milwaukee, WI, USA; [5]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [6]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of South Korea; [7]Norton Cancer Institute, Norton Health Care, Louisville, KY, USA; [8]Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of South Korea; [9]AstraZeneca, Waltham, MA, USA; [10]AstraZeneca, South San Francisco, CA, USA; [11]AstraZeneca, Cambridge, UK; [12]Ancora Biotech, Inc., Palo Alto, CA, USA; [13]Lemieux Center for Blood Cancers, UPMC Hillman Cancer Center, Pittsburgh, PA, USA

Most FL patients had heavily pre-treated, high risk disease

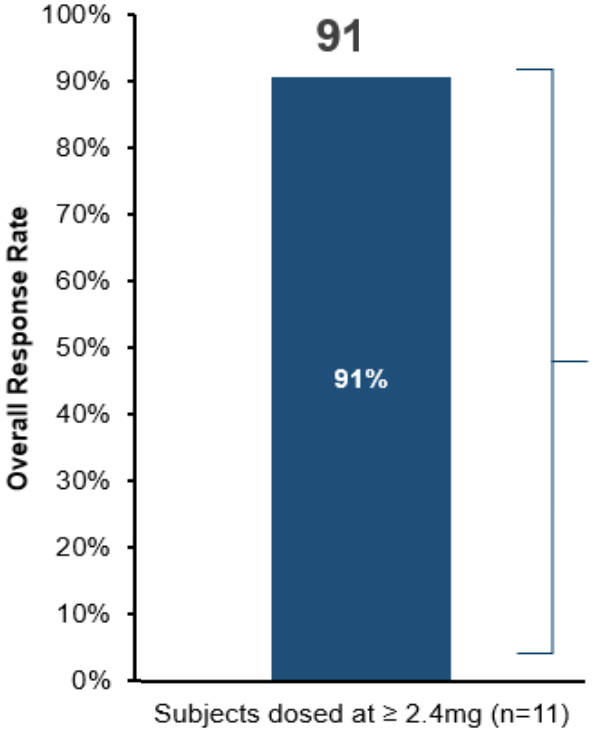
Baseline Characteristics	N =17
Median age, years (range)	64 (33-86)
Ann Arbor stage III-IV, n (%)	11 (64.7)
CD20 negative disease	**5 (29.4)**
POD24, n (%)	**9 (52.9)**
Refractory to last line of treatment	4 (23.5)
Prior lines of therapy, median (range) **≥ 3 lines, n (%)**	3 (2-9) **12 (70.6)**
Types of prior treatment, n (%)	
Alkylating agent	13 (76.5)
Anti-CD20 mAb	17 (100.0)
IMiD	8 (47.1)
CD19-directed CAR-T	**2 (11.8)**
CD20-directed TCE	**2 (11.8)**
Autologous HSCT	1 (5.9)



Clinical cut-off date: December 31, 2022

CART, chimeric antigen receptor T-cell therapy; CD20, cluster of differentiation 20; ECOG PS, Eastern Cooperative Oncology Group Performance status; HSCT, hematopoietic stem cell transplant; IMiD, immunomodulating drug; mAB, monoclonal antibody; POD24, progression of disease in 24 months

High complete response rate reported by IRC

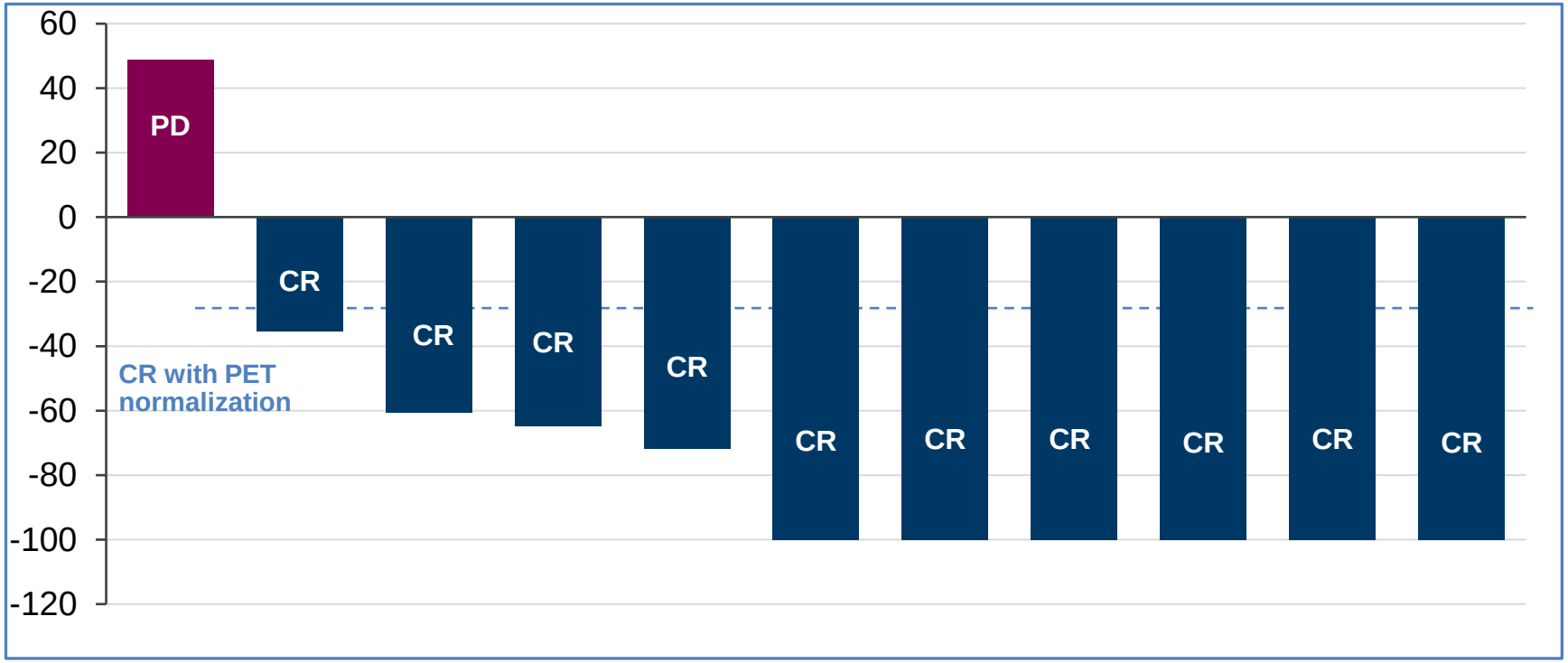


- **ORR / CR rate 91% (10/11)** at target **doses of ≥2.4 mg**
- Out of 5 CR patients with available samples, **all were MRD negative by NGS**

n=11	ORR	CR
CD20 negative status, n (%)	2/2 (100%)	2/2 (100%)
Prior CD20 TCE	2/2 (100%)	2/2 (100%)
POD24, n (%)	5/5 (100%)	5/5 (100%)
≥ 4 prior lines	3/4 (75%)	3/4 (75%)

Data refers to efficacy evaluable subset. CD20; cluster of differentiation 20; CR, complete response; IRC, independent radiological review committee; MRD, minimal residual disease; ORR, overall response rate; POD24, progression of disease in 24 months, TCE, T-cell engagers

Best response in patients treated at ≥ 2.4 mg



Responses by RECIL 2017; CR, complete response; ORR, overall response rate; PD, progressive disease

Double Step-up Dosing (2SUD) Regimen Mitigates Severe ICANS and CRS While Maintaining High Efficacy in Subjects With Relapsed/Refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) Treated With AZD0486, a Novel CD19xCD3 T-cell engager (TCE): Updated Safety and Efficacy Data From the Ongoing First-in-Human (FIH) Phase 1 trial

Sameh Gaballa[1], Ranjit Nair[2], Ryan Jacobs[3], Sumana Devata[4], Seok-Goo Cho[5], Don Stevens[6], Dok Hyun Yoon[7], Nirav Shah[4], Denise Brennan[8], David Sermer[9], Rob Chen[10], Jason Law[8], Robin Lesley[11], Ben Buelow[12], Alessandra Forcina[10], and Jing-Zhou Hou[13]

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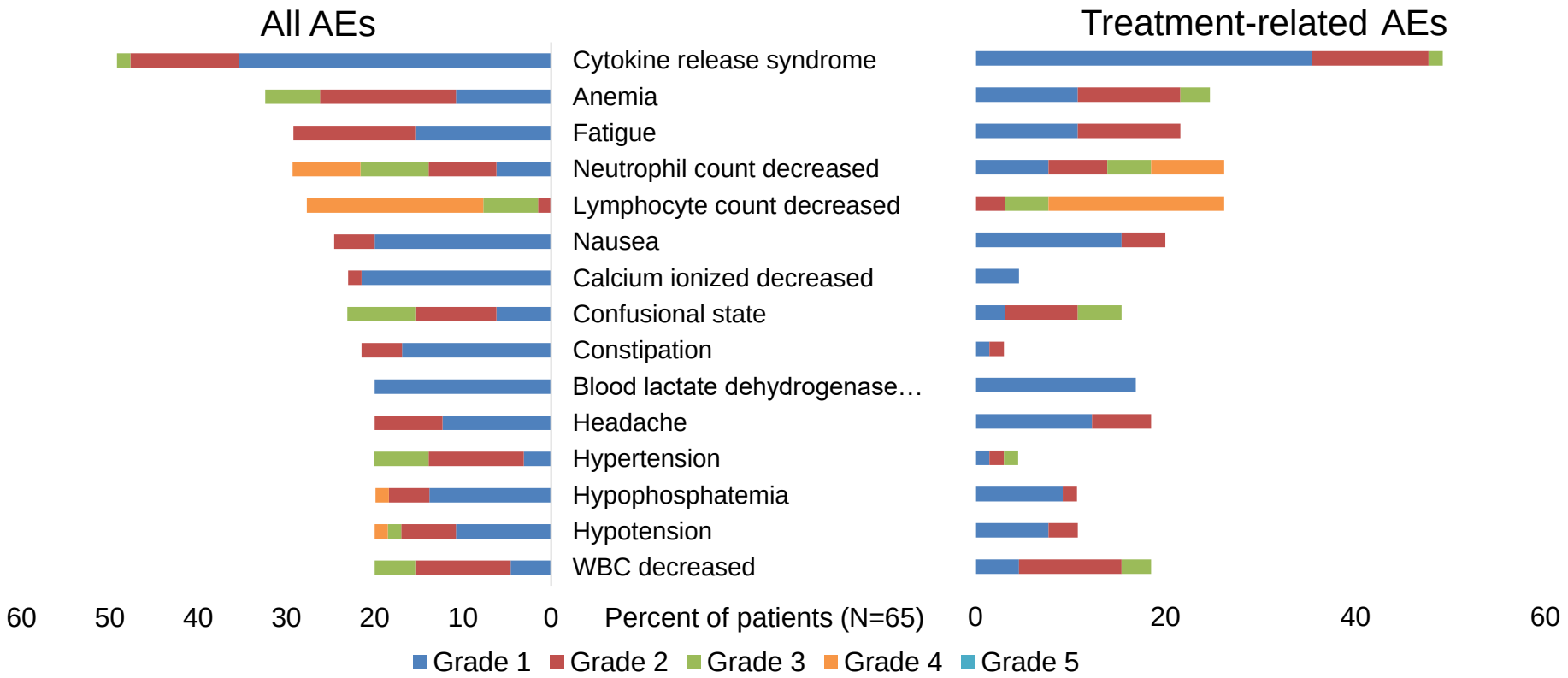
[1]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Atrium Health Levine Cancer Institute, Charlotte, NC: [4]Medical College of Wisconsin, Milwaukee, WI; [5]Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [6]Norton Cancer Institute, Norton Health Care, Louisville, KY; [7]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [8]AstraZeneca, Waltham, MA; [9]AstraZeneca, New York, NY; [10]AstraZeneca, Cambridge, UK; [11]AstraZeneca, South San Francisco, CA; [12]Ancora Biotech, Inc., Palo Alto, CA; [13]Lemieux Center for Blood Cancers, UPMC Hillman Cancer Center, Pittsburgh, PA

Demographic and Baseline Characteristics

Characteristic	N=65
Age, median (range), y	68 (22–86)
Male, n (%)	38 (58.5)
ECOG PS at study entry, n (%)	
0	27 (41.5)
1–2	38 (58.5)
Ann Arbor stage III–IV, n (%)	49 (75.4)
CD20-negative, n (%)	17 (26.2)
Median prior lines of therapy (range)	3 (2–21)
2 lines, n (%)	14 (21.5)
≥3 lines, n (%)	49 (75.4)
Unknown	2 (3.1)
Type of lymphoma	
DLBCL/HGBL	29 (44.6)
MCL	5 (7.7)
FL	26 (40.0)
MZL	4 (6.2)
Other	1 (1.5)

Characteristic	N=65
Refractory to last line of therapy, n (%)	22 (33.8)
Prior types of treatment, n (%)	
CD19-directed CAR T	16 (24.6)
CD20 T-cell engager	3 (4.6)
IMiD	17 (26.2)
Allogeneic SCT	4 (6.2)
Autologous SCT	3 (4.6)

AEs Affecting ≥20% of Patients vs Treatment-related AEs



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Patient Disposition

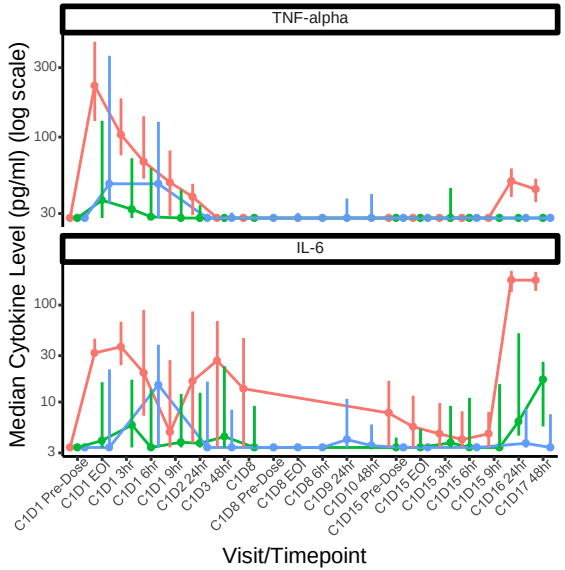
	N=65
Reasons for discontinuing treatment, n (%)	32 (49.2)
Disease progression	23 (35.4)
Physician decision	3 (4.6)
Withdrawal of consent	2 (3.1)
Death[a]	1 (1.5)
Other[b]	1 (1.5)
Drug-related AE[c]	0

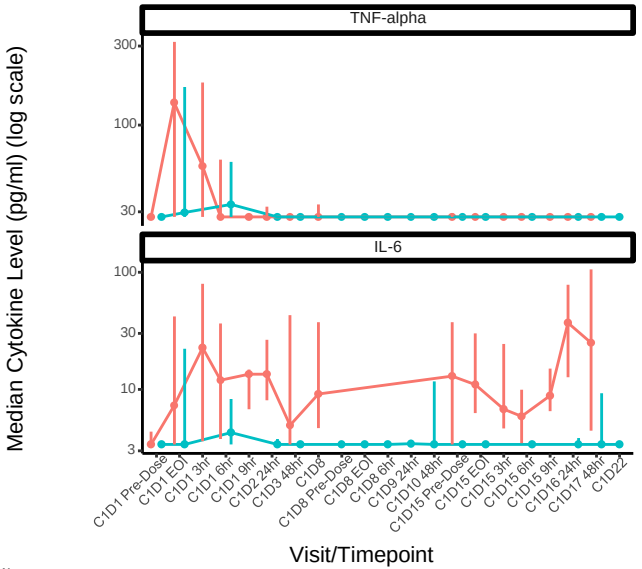
[a]One patient died due to COVID-19 infection that was not considered by the investigator to be treatment related.
[b]After achieving a CR, patient received allogeneic SCT
[c]One patient discontinued treatment due to an AE of COVID-19 that was not considered by the investigator to be treatment-related; the patient died and never resumed treatment.

Reduction of CRS and ICANS Events in Patients Treated in the Double SUD Cohorts Compared With Fixed and Single SUD Cohorts

	CRS			ICANS		
	DLBCL/HGBL and FL Treated at Target Doses of 2.4 mg and 7.2 mg (N=44)					
Grade	Fixed n=5 (% of total)	1 SUD n=19 (% of total)	2 SUD n=20 (% of total)	Fixed n=5 (% of total)	1 SUD n=19 (% of total)	2 SUD n=20 (% of total)
Grade 1–2	5 (100)	10 (52.6)	**6 (30.0)**	1 (20.0)	3 (15.8)	**1 (5.0)**
Grade 3	0	0	**0**	1 (20.0)	3 (15.8)	**0**

Cytokine Levels After Target Dose With Double SUD Compared With Fixed Dosing and Single SUD





Data show median and interquartile range

All Subtypes

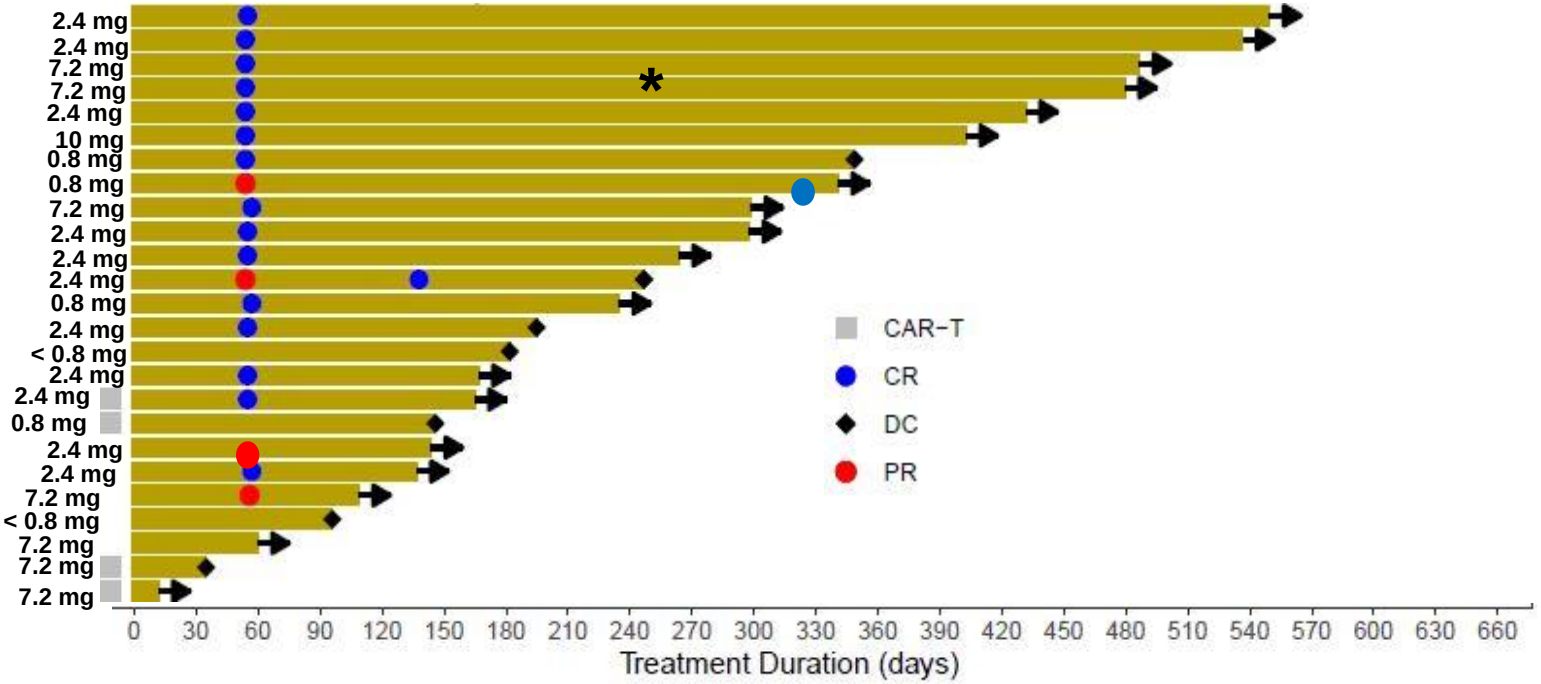
2400 µg target dose cohorts

- 5a (n=6): No priming dose
- 5b (n=14): 270µg priming C1D1, 2400µg target C1D15
- 5d (n=7): 270µg priming C1D1, 1000µg step-dose C1D8, 2400µg target C1D15

7200 µg target dose cohorts

- 6a (n=8): 1000µg priming C1D1, 7200µg target C1D15
- 6d (n=10): 270µg priming C1D1, 1000µg step-dose C1D8, 7200µg target C1D15

Duration of Treatment for Patients With FL – ASH 2023 Update



*PD at cycle 9 but converted back to CR.

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Response Rates of Treatment for Patients With FL – ASH 2023 Update

AZD0486[1]	2.4mg	7.2mg	TD ≥ 0.8
Evaluable	14	7	27
ORR	(14/14) 100%	(6/7) 86%	(25/27) 93%
CR	(12/14) 86%	(5/7) 71%	(21/27) 78%

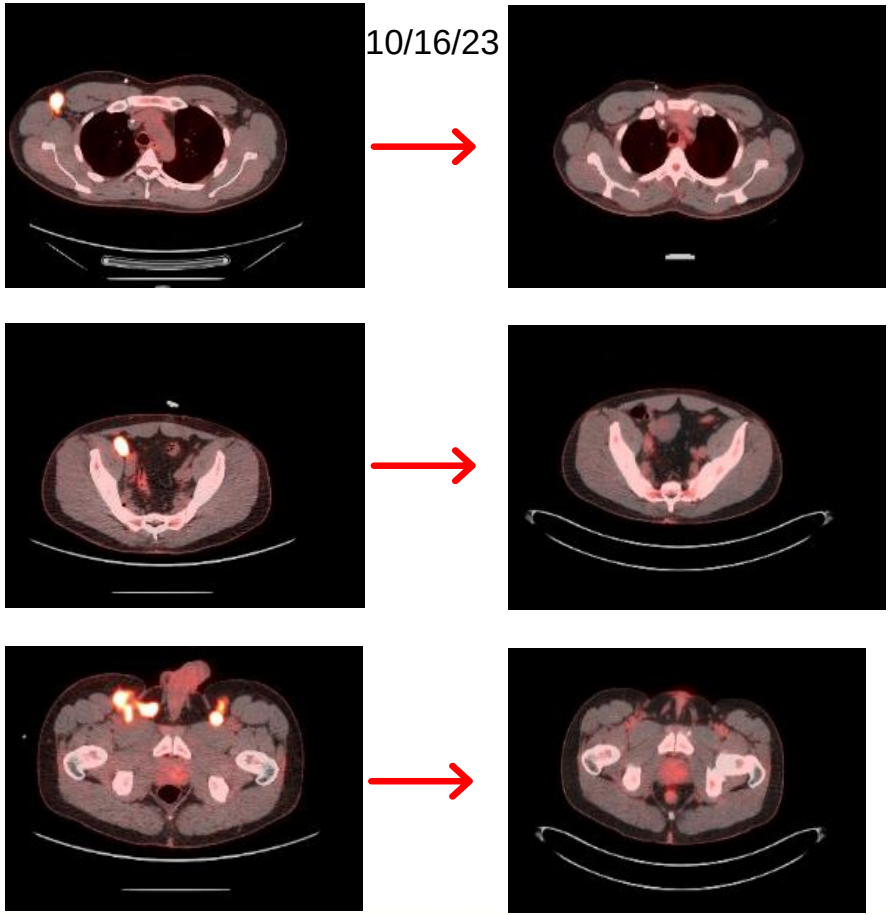
	Mosunetuzumab[2]	Odronextamab[3]
ORR	80%	81%
CR	60%	75%

12-mo DOR (%)		
AZD0486[1]	Mosunetuzumab[2]	Odronextamab[3]
82%	62%	69%

1. S Gaballa et al. ASH 2023. 2. Budde et al, *Lancet Oncol* (2022) 23: 1055-65; 3. Kim et al, *Blood* (2022) 140 (Supplement 1): 2280-2282

Patient RMN

- 32 y/o Hispanic male with FL
- POD 24 following RCHOP while on rituxan maintenance
- Refractory to 2L therapy on GCT3010-02 with Epco+Rev+Ritux
- Enrolled on TNB486 9/13/22 at 2.4mg cohort with single SUD.
- Had G3 ICANS with confusion at first 2.4mg dose
  - Resolved within 48 hours.
- Last PET CT 10/16/23 with ongoing CR.



Conclusions and Future Directions

- With double SUD, AZD0486 appears safe with low CRS and ICANS
- High CR rates in FL at current doses
- Expand enrollment of DLBCL at 15mg and add additional dose levels
- Will explore subcutaneous dosing for patient convenience
- Separate DLBCL and FL Phase 2 trial planned when RP2D is reached
- Exploration into other disease subtypes
    - CLL
    - MCL
    - ALL